DETAILED ACTION

Applicant's responses filed on 08/04/2011 and on 07/19/2011 have been entered.

The declaration signed by David B. Weiner filed on 08/04/2011 has been considered.

Claims 2-13, 18, 20-54, 61-65, and 72-76 are cancelled. Claims 1, 14-17, 19, 55-60, 66-71 and 77 are pending.

It is noted that as Applicant elected "cytokine" as the species recited in claim 1 and "IL-15" as the species recited in claim 77 in the reply filed on 11/09/2010.

Claims 1, 14-17, 19, 55-60, 66-71 and 77 are currently under examination to the extent of elected species, cytokine IL-15.

This application, 10/560,650, is a 371 of PCT/US04/18962 filed on 06/14/2004, which claims benefit of provisional application 60/478,205 filed on 06/13/2003 and claims benefit of provisional application 60/478,210 filed on 06/13/2003.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1, 14, 16, 17, 19, 55, 56, 58-60, 66, 67, 69-71 and 77 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Yang et al.** (Yang et al., Induction of potent Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-

NY1999). *J Infect Dis.* 184(7):809-16, 2001) in view **Letvin et al.** (WO 99/16466, international publication date 04/08/1999) and **Levinson et al.** (US 2006/0052592, publication date 03/09/2006, PCT/US03/19383 filed on 06/20/2003, provisional application No: 60/390,304 filed on 06/20/2002) and **Meazza et al.** (Meazza et al., Expression of two interleukin-15 mRNA isoforms in human tumors does not correlate with secretion: role of different signal peptides, *Eur J Immunol.* 27(5):1049-54, 1997; this reference has been cited by Applicant in the IDS filed on 08/31/2010). Applicant's arguments filed on 08/04/2011 and on 07/19/2011 have been fully considered and found not persuasive. Previous rejection is ***maintained*** for the reasons advanced on pages 6-18 of the office action mailed on 01/19/2011.

For the clarity of record, the rejection for the reasons advanced on pages 6-18 of the office action mailed on 01/19/2011 is reiterated below.

Claim 1 filed on 11/12/2010 is directed to an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of: (i) a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein; and (ii) a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating cytokine.

Claim 14 is directed to the isolated nucleic acid molecule of claim 1 wherein said isolated nucleic acid molecule is a plasmid.

Claim 16 is directed to a composition comprising a nucleic acid molecule of claim 1 and a nucleic acid molecule that comprises a nucleic acid sequence that encodes an immunogen.

Claim 17 is directed to the composition of claim 16 wherein said composition comprises a nucleic acid molecule that encodes an immunogen, wherein said immunogen is a

pathogen antigen, a cancer-associated antigen or an antigen linked to cells associated with autoimmune diseases.

Claim 19 is directed to the composition of claim 17 wherein said immunogen is a pathogen antigen is from a pathogen selected from the group consisting of HIV, HSV, HCV, and WNV.

Claim 55 is directed to the isolated nucleic acid molecule of claim 1 comprising a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein.

Claim 56 is directed to the isolated nucleic acid molecule of claim 55 wherein said isolated nucleic acid molecule is a plasmid.

Claim 58 is directed to a composition comprising a nucleic acid molecule of claim 55 and a nucleic acid molecule that comprises a nucleic acid sequence that encodes an immunogen.

Claim 59 is directed to the composition of claim 58 wherein said composition comprises a nucleic acid molecule that encodes an immunogen, wherein said immunogen is a pathogen antigen, a cancer-associated antigen or an antigen linked to cells associated with autoimmune diseases.

Claim 60 is directed to the composition of claim 59 wherein said immunogen is a pathogen antigen is from a pathogen selected from the group consisting of HIV, HSV, HCV, and WNV.

Claim 66 is directed to the isolated nucleic acid molecule of claim 1 comprising a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide wherein the non-IgE protein is an immunomodulating protein.

Claim 67 is directed to the isolated nucleic acid molecule of claim 66 wherein said isolated nucleic acid molecule is a plasmid.

Claim 69 is directed to a composition comprising a nucleic acid molecule of claim 66 and a nucleic acid molecule that comprises a nucleic acid sequence that encodes an immunogen.

Claim 70 is directed to the composition of claim 69 wherein said composition comprises a nucleic acid molecule that encodes an immunogen, wherein said immunogen is a

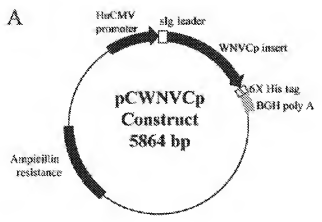
pathogen antigen, a cancer-associated antigen or an antigen linked to cells associated with autoimmune diseases.

Claim 71 is directed to the composition of claim 70 wherein said immunogen is a pathogen antigen is from a pathogen selected from the group consisting of HIV, HSV, HCV, and WNV.

Claim 77 is directed to the isolated nucleic acid molecule of claim 1, wherein the non-IgE protein is an immunomodulating protein IL-15.

Claim interpretation: **(I)** It is noted that the limitation "a nucleic acid sequence selected from the group consisting of" clearly indicates that the limitation (i) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein" and the limitation (ii) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof" are two different species that can be selected from to be the claimed "isolated nucleic acid". In other words, the art is required to discloses either the limitation (i) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein" or the limitation (ii) "a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide, wherein the non-IgE protein is an immunomodulating protein selected from the group consisting of cytokines, chemokines, cellular death receptors, cellular adhesion molecules, cellular growth factors, cellular growth factor receptors, protein kinases and enzymes or functional fragment thereof". **(II)** In the absence any peptide sequence encoded by a nucleic acid sequence disclosed in specification and/or recited in the claims, the limitation "an IgE signal peptide" encompass any variant of signal peptide of an immunoglobulin E (IgE).

With regard to claims 1, 14, 16, 17, 19, 55, 56, 58-60, 66, 67, 69-71 and 77, **Yang et al.** teaches induction of potent Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-NY1999) (See title, Yang et al., 2001). Yang et al. teaches that West Nile virus (WNV) is a vector borne pathogen that induces brain inflammation and death. Recently, confirmed cases of infection and deaths have occurred in the United States Mid-Atlantic region. Yang et al. teaches a DNA vaccine encoding the WNV capsid protein was constructed, and the *in vivo* immune responses generated were investigated in DNA vaccine-immunized mice. Antigen-specific *humoral and cellular immune responses* were observed, including a potent induction of antigen-specific Th1 and cytotoxic T lymphocyte responses. Strong induction of Th1-type immune responses *included high levels of antigen-specific elaboration of the Th1-type* ***cytokines*** *interferon-gamma and interleukin-2* and beta-chemokines RANTES (regulated upon activation, normal T cell-expressed and secreted) and macrophage inflammatory protein-1beta. Dramatic infiltration of CD4 and CD8 T cells and macrophages also was observed at the muscle injection site. Yang et al. states that these results support the potential utility of this method as a tool for developing immunization strategies for WNV and other emerging pathogens (See abstract, Yang et al., 2001). Furthermore, Yang et al. teaches a recombinant DNA vaccine, a plasmid construct, as a composition comprises a nucleic acid sequence encoding the *human immunoglobulin secretory leader signal* (See sIg leader, indicated in Figure 1A, page 810, Yang et al., 2001, and the plasmid map provided below) fused West Nile Virus (WNV) capsid protein (Cp).



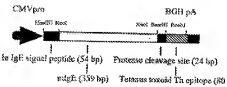
Yang et al. does not *explicitly* teach **(i)** the limitation "from the same species as the non-IgE protein" recited in claims 1 and 55, and **(ii)** the limitation the immunomodulating protein is a cytokine recited in claim 1 and the limitation the non-IgE protein is an immunomodulating protein is IL-15 recited in claim 77, **(iii)** the limitation "IgE signal peptide" recited in claims 1, 55 and 66.

With regard to **(i)** the limitation "from the same species as the non-IgE protein" recited in claims 1 and 55, and **(ii)** the limitation the immunomodulating protein is a cytokine recited in claim 1 and the limitation the non-IgE protein is an immunomodulating protein is IL-15 recited in claim 77, **Letvin et al.** (WO 99/16466) teaches a vaccine composition having a mammalian *cytokine fusion protein* (e. g., murine or *human*) or a homologue or analogous protein thereof, as described herein. Accordingly, the claimed invention embodies a vaccine composition having the nucleic acid sequence (e. g., SEQ ID NO : 1 or 3) that codes for a cytokine fusion protein. The vaccine composition also comprises the cytokine fusion protein comprising the amino acid sequence of SEQ ID NO: 2 or 4, or an amino acid sequence encoded by SEQ ID NO : 1 or 3, or a homolog thereof (See for instance, lines 3-10 of page 14, Letvin et al., 1999). Letvin et al.

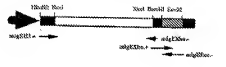
teaches the immunologic effects of co-administering protein and plasmid cytokines with an HIV-1 gpl20 DNA vaccine in mice. Administering plasmid cytokines before or with gpl20 DNA decreased gpl20-specific antibody titers and T cell functional activity, whereas *administering plasmid cytokines after gpl20 DNA augmented gpl20-specific immune responses.* These results demonstrate that antigen-cytokine timing is a critical parameter in determining the overall biologic effect of the cytokine. Moreover, IL-2/Ig was significantly more effective than IL-2 in augmenting DNA vaccine-elicited immune responses, indicating that the Ig fusion markedly enhances the adjuvant properties of this cytokine (See for instance, lines 3-10 of page 18, Letvin et al., 1999). Letvin et al. teaches the use of plasmid-expressed cytokines as a strategy for ***augmenting*** *immune responses* elicited by plasmid DNA vaccines and the cytokine may be e.g. IL-2, GM-CSF, IL-4, IL-6, IL-7, IL-13, IL-10, IL-12, **IL-15**, TNF-alpha or IFN-gamma (See for instance, lines 14-18 of page 11, lines 20-29 of page 18, and Example 13 on pages 35-36, Letvin et al., 1999).

With regard to **(iii)** the limitation "IgE signal peptide" recited in claims 1, 55 and 66, **Levinson et al.** teaches human IgE signal peptide in the construction and *in vitro* expression of human IgE tetanus fusion protein (See Figure 2, Levinson et al., US 2006/0052592, shown below, which is also disclosed in Figure 2 of provisional application No: 60/390,304 filed on 06/20/2002).

A. Human mIgE - Tetanus toxoid fusion protein expression cassette



B. PCR amplification with specific primer set



With regard to IL-15 recited in claim 77 and the endogenous signal peptide present in human IL-15, **Meazza et al.** teaches that Interleukin (1L)-15 is a four-helix bundle cytokine sharing several biological properties with IL-2. By reverse transcriptase-polymerase chain reaction analysis, human cancer cell lines of different histotypes are shown to express two IL-15 amplification products: a 524-bp band corresponding to the IL-15 mRNA found in macrophages, and another of 643 bp corresponding to an alternatively spliced mRNA including a 119-bp alternative exon. IL-15 was undetectable in the supernatant of tumor cell lines expressing either one or both of the mRNA isoforms as evaluated by a bioassay or by ELISA, indicating that IL-15 is not secreted. However, IL-15 could be detected intracellularly in some tumor cells by confocal microscopy analysis. Since the pre-proteins encoded by the two mRNA isoforms differ in the signal peptide sequence, we have analyzed the characteristics of these signal peptides and their possible role in controlling secretion. The two IL-15 cDNA isoforms, expressed in COS-7 cells, induced very low levels of IL-15 secretion. However, *substitution of the sequence encoding natural signal peptide(s) with the one from IgVx chain in the IL-15 cDNA results in a*

significantly higher secretion of biologically active IL-15 (15-30-fold) upon cDNA transfection.

A poor efficiency of natural signal peptides may represent one of the mechanisms involved in the control of IL-15 secretion (See abstract, Fig. 4 shown below, Meazza et al., 1997).

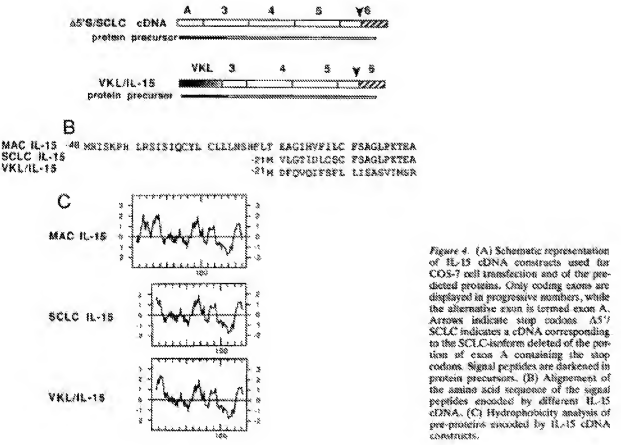


Figure 4. (A) Schematic representation of IL-15 cDNA constructs used for COS-7 cell transfection and of the predicted proteins. Only coding exons are displayed in progressive numbers, while the alternative exon is termed exon A. Arrows indicate stop codons. A5'/ SCLC indicates a cDNA corresponding to the SCLC-isoform deleted of the portion of exon A containing the stop codons. Signal peptides are darkened in protein precursors. (B) Alignement of the amino acid sequence of the signal peptides encoded by different IL-15 cDNA. (C) Hydrophobicity analysis of pre-proteins encoded by IL-15 cDNA constructs.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Yang et al. regarding a recombinant DNA vaccine, a plasmid construct, as a pharmaceutical composition comprises a nucleic acid sequence encoding the human immunoglobulin secretory leader signal (See sIg leader, indicated in Figure 1A, Yang et al., 2001, and the plasmid map provided below) fused West Nile Virus (WNV) capsid protein (Cp), with the teachings of (i) Letvin et al. regarding the use of plasmid-expressed human cytokine IL-15 as a strategy for augmenting immune responses elicited by

plasmid DNA vaccines, (ii) Levinson et al. regarding human IgE signal peptide in the construction and *in vitro* expression of human IgE tetanus fusion protein, and (iii) Meazza et al. regarding substitution of the sequence encoding natural human IL-15 signal peptide(s) with the signal peptide from IgVx chain in the IL-15 cDNA results in a significantly higher secretion of biologically active IL-15 upon cDNA transfection, to arrive at isolated nucleic acid recited in claims 1, 14, 16, 17, 19, 55, 56, 58-60, 66, 67, 69-71 and 77 of instant application by substitution of WNVCp encoding sequences taught by Yang et al. with IL-15 coding sequence and fused to either sIg leader taught by Yang et al. or fused to human IgE signal peptide taught by Levinson et al. for expression of human IL-15 with desired secretion level taught by Meazza et al., in the context of the plasmid taught by either Yang et al. (2001) or Letvin et al. (1999).

One having ordinary skill in the art would have been motivated to combine the teachings of Yang et al., Letvin et al., Levinson et al., and Meazza et al. because (i) Letvin et al. specifically teaches the expression of cytokines, including IL-15 and IL-2, as a strategy for augmenting immune responses elicited by plasmid DNA vaccines, (ii) Levinson et al. teaches human IgE signal peptide in the construction and *in vitro* expression of human IgE-tetanus fusion protein, and (iii) Meazza teaches substitution of the sequence encoding natural human IL-15 signal peptide(s) with the signal peptide from IgVx chain in the IL-15 cDNA results in a significantly higher secretion of biologically active IL-15 upon cDNA transfection. The combined teachings of Yang et al., Letvin et al., Levinson et al., and Meazza et al. demonstrate using an IgE signal peptide for expression of a non-IgE protein, such as human cytokine IL-15, at a desired secretion level from an isolated nucleic acid molecule, such as a DNA vaccine.

There would have been a reasonable expectation of success given (i) successful demonstration of the induction of potent Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-NY1999) and release of various cytokines by T-cells of immunized mice, by the teachings Yang et al. (See Figure 3, Yang et al., 2001), (ii) successful demonstration of IL-2/Ig fusion protein in enhancement of antigp120 immune response elicited by pV1-gp120, by the teachings of Letvin et al. (See Example 8, pages 26-29), and (iii) successful demonstration of human IgE signal peptide in the construction and *in vitro* expression of human IgE tetanus fusion protein, by the teachings of Levinson et al., and (iv) successful demonstration of substitution of the sequence encoding natural human IL-15 signal peptide(s) with the signal peptide from IgVx chain in the IL-15 cDNA results in a significantly higher secretion of biologically active IL-15 upon cDNA transfection, by the teachings of Meazza et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) [available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf; and *KSR Guidelines Update* has been published in the Federal Register at 75 *Fed. Reg.* 53643-60 (Sep. 1, 2010) and is posted at USPTO's internet Web site at http://www.uspto.gov/patents/law/notices/2010.jsp]. The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine Yang

et al., Letvin et al., Levinson et al. and Meazza et al. has been clearly set forth above in this office action.

It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant's arguments

(I) Applicant states that the Levinson application, US 2006/0052592, which was published March 9, 2006 is a national stage application of PCT/US03/19383 filed on June 20, 2003 which itself claims priority to provisional application No: 60/390,304 filed on June 20, 2002. Accordingly, the Levinson application was not published until after the effective filing date of the instantly claimed invention and only qualifies as prior art under 35 U.S.C. 102(e), as noted in the Official Action, Figure 2 in Levinson is disclosed in the provisional application filed June 20, 2002 to which Levinson claims priority.

(II) Applicant states that the Declaration of David B. Weiner states that co-inventors in Levinson did not conceive of or contribute to the conception of using IgE leader sequences in fusion proteins. The Declaration of David B. Weiner states that the conception of using IgE leader sequences in fusion proteins which comprise protein sequences derived from the same species and of genetic constructs which encode fusion proteins having IgE leader sequence linked to protein sequences derived from the same species were conceived by him and his co-inventors prior to the effective filing date of Levinson. In addition, the Declaration of David B. Weiner states that the conception of using IgE leader sequences in fusion proteins which comprise immunomodulatory protein sequences and of genetic constructs which encode fusion proteins having IgE leader sequence linked to immunomodulatory protein sequences were conceived by him and his co-inventors prior to the effective filing date of Levinson. The Declaration of David B. Weiner establishes that the disclosure of subject matter in Levinson regarding the use of the IgE leader sequence is the invention of the currently named inventors and that as disclosed in Levinson in the vaccines against IgE mediated allergy disclosed in

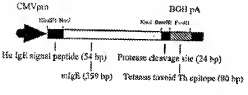
Levinson the use of IgE leader was derived from the invention of the current inventors The relevant portion of Levinson is was derived from Applicants' own work and therefore not prior art under 35 U.S.C. 102(e) (see In re Mathews, 408 F.2d 1393, 161 USPQ 276 (CCPA 1969) and In re DeBaun, 687 F.2d 459, 214 USPQ 933 (CCPA 1982)).

For the foregoing reasons, Applicants request that the rejection of claims 1, 14, 16, 17, 19, 55, 56, 58-60, 66, 67, 69-71 and 77 under 35 U.S.C. 103(a) as being unpatentable over Yang et al. in view Letvin et al. and Levinson et al. and Meazza et al. be withdrawn (See page 8 of Applicant's response filed on 07/19/2011.

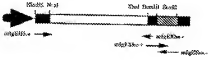
Response to Applicant's arguments

(I) As stated in the maintained rejection, **Levinson et al.** teaches human IgE signal peptide in the construction and *in vitro* expression of human IgE tetanus fusion protein (See Figure 2, Levinson et al., US 2006/0052592, shown below, which is also disclosed in Figure 2 of provisional application No: 60/390,304 filed on 06/20/2002).

A. Human mIgE - Tetanus toxoid fusion protein expression cassette



B. PCR amplification with specific primer set



As provisional application No: 60/390,304 filed on 06/20/2002 (which Levinson et al. US 2006/0052592 claims benefits from) is before the earliest priority date 06/13/2003 (the filing

date of provisional application 60/478,205 and provisional application 60/478,210 from which instant application claim benefits). Levinson et al. is a prior art under with 102(e) date.

(II) It is noted that there are four inventors listed in the Levinson et al. (US 2006/0052592): **Arnold I Levinson**, **Sandra Calarota**, David B Weiner, and **Miguel Otero**. Among these listed four inventors, David B Weiner is the only inventor listed in instant application.

The following M.P.E.P statements are directly relevant to the declaration signed by David B. Weiner filed on 08/04/2011.

716.10 Attribution

Under certain circumstances an affidavit or declaration may be submitted which attempts to attribute an activity, a reference or part of a reference to the applicant. If successful, the activity or the reference is no longer applicable. When subject matter, disclosed but not claimed in a patent application filed jointly by S and another, is claimed in a later application filed by S, the joint patent or joint patent application publication is a valid reference available as prior art under **35 U.S.C. 102**(a), **(e),** or (f) unless overcome by affidavit or declaration under **37 CFR 1.131** showing prior invention (see **MPEP § 715**) or an unequivocal declaration by S under **37 CFR 1.132** that he or she conceived or invented the subject matter disclosed in the patent or published application. Disclaimer by the other patentee or other applicant of the published application should not be required but, if submitted, may be accepted by the examiner.

Where there is a published article identifying the authorship (**MPEP § 715.01(c)**) or a patent or an application publication identifying the inventorship (**MPEP § 715.01(a)**) that discloses subject matter being claimed in an application undergoing examination, the designation of authorship or inventorship does not raise a presumption of inventorship with respect to the subject matter disclosed in the article or with respect to the subject matter disclosed but not claimed in the patent or published application so as to justify a rejection under **35 U.S.C. 102(f)**.

However, it is incumbent upon the inventors named in the application, in response to an inquiry regarding the appropriate inventorship under **35 U.S.C. 102(f)** or to rebut a rejection under **35 U.S.C. 102**(a), **(e),** or (f), to provide a satisfactory showing by way of affidavit under **37 CFR 1.132** that the inventorship of the application is correct in that the reference discloses subject matter derived from the applicant rather than invented by the author, patentee, or applicant of the published application notwithstanding the authorship of the article or the inventorship of the patent or published application. *In re Katz*, 687 F.2d 450, 455, 215 USPQ 14, 18 (CCPA 1982) (inquiry is appropriate to clarify any ambiguity created by an article regarding inventorship and it is then incumbent upon the applicant to provide "a satisfactory showing that would lead to a reasonable conclusion that [applicant] is the ... inventor" of the subject matter disclosed in the article and claimed in the application).

An uncontradicted ***"unequivocal statement"*** from the applicant regarding the subject matter disclosed in an article, patent, or published application will be accepted as establishing inventorship. *In re DeBaun*, 687 F.2d 459, 463, 214 USPQ 933, 936 (CCPA 1982). However, a statement by the applicants regarding their inventorship in view of an article, patent, or published application may not be sufficient where there is evidence to the contrary. *Ex parte Kroger*, 218 USPQ 370 (Bd. App. 1982) (a rejection under **35 U.S.C. 102(f)** was affirmed notwithstanding declarations by the alleged actual inventors as to their inventorship in view of a nonapplicant author submitting a letter declaring the author's inventorship); *In re Carreira*, 532 F.2d 1356, 189 USPQ 461 (CCPA 1976) (disclaiming declarations from patentees were directed at the generic invention and not at the claimed species, hence no need to consider derivation of the subject matter).

A successful **37 CFR 1.132** affidavit or declaration establishing derivation by the author, patentee, or applicant of the published application of a first reference does ***not*** enable an applicant to step into the shoes of that author, patentee, or applicant of the published application in regard to its date of publication so as to defeat a later second reference. *In re Costello*, 717 F.2d 1346, 1350, 219 USPQ 389, 392 (Fed. Cir. 1983).

The declaration signed by David B. Weiner filed on 08/04 2011 declare the following statements:

(i) "4. Prior to the effective filing date for United States Patent Application Serial No. 10/518,701 of I June 20, 2002, my co-inventors in United States Patent Application Serial No. 10/560,650 and I conceived of genetic construct that encode fusion proteins comprising the IgE signal peptide fused to no-IgE protein from the same species".

With regard to these statements, there is no ***evidence*** on the record supports that "Prior to the effective filing date for United States Patent Application Serial No. 10/518,701 of June 20, 2002", Applicant (David B. Weiner) conceived of genetic construct that encode fusion proteins comprising the IgE signal peptide fused to no-IgE protein from the same species.

(ii) "5. The subject matter disclosed in United States Patent Application Serial No. 10/518,701 which relates to genetic constructs that encode fusion proteins comprising the IgE signal peptide fused to an immunomodulating protein was conceived by my co-inventors in United States Patent Application Serial No. 10/560,650 and me. My co-inventors in United States Patent Application Serial No. 10/518,701 did not conceive of that subject matter".

"6. The subject matter disclosed in United States Patent Application Serial No. 10/518,701 which relates to using genetic constructs that encode fusion proteins comprising the IgE signal peptide to enhance expression of a target protein was from the work by my co-inventors and me in United States Patent Application Serial No. 10/560,650. My co-inventors in United States Patent Application Serial No. 10/518,701 did not conceive of using IgE signal peptide in the fusion proteins disclosed in United States Patent Application Serial No. 10/518,701".

The declaration field by David B. Weiner filed on 08/04 2011 does not provide *"unequivocal statement"* because it remains equivocal what are the contribution of Arnold I Levinson, Sandra Calarota, and Miguel Otero in prior art Levinson et al. (US 2006/0052592). It is noted that the contribution of listed inventors on Levinson et al. (US 2006/0052592) does not necessarily be the *conception* of "the IgE signal peptide fused to no-IgE protein from the same species" as the stated in the declaration signed by David B. Weiner. In this regard, it is worth noting that the claimed subject matter of Levinson et al. (US 2006/0052592) reads on "An

isolated nucleic acid molecule that encodes protein comprising at least one epitope of membrane IgE and being free of epitopes of serum IgE" (See claim 1 and Figure 2 of US application 10/518,701, US 2006/0052592), which clearly encompasses the epitope of IgE signal peptide recited in the claims of instant application. Furthermore, inventor Levinson et al. is the co-author of Cines et al. that discloses purification and characterization of IgE (See abstract, Table 1 and Figure 7, Cines et a., *In vitro* binding of an IgE protein to human platelets, *J. Immunol.* 136(9):3433-40, 1986). On the other hand, the declaration signed by David B. Weiner does not provide any information regarding the relationship (for instance, conditions under 103(c) prior art exclusion) between third co-inventor David B. Weiner, and the rest of inventors, first co-inventor, Arnold I Levinson, second co-inventor Sandra Calarota, and fourth co-inventor Miguel Otero, in the context of claimed subject matter stated in the prior art Levinson et al. (US 2006/0052592). Further, there is no evidence on the record that co-inventors, Arnold I Levinson (first inventor), Sandra Calarota (second inventor), and Miguel Otero (fourth inventor) are under supervision of David B. Weiner (third inventor) in the context of claimed subject matter of US application 10/518,701, which is publication US 2006/0052592.

For the reasons discussed above, the Examiner maintains the position that art Levinson et al. (US 2006/0052592) remains a valid prior art having a 102(e) date with inventors "*by another*".

2. Claims 1, **15**, 55, **57**, 66, and **68** remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Yang et al.** (Yang et al., Induction of potent Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-NY1999). *J Infect Dis.* 184(7):809-16, 2001) in view **Letvin et al.** (WO 99/16466, international publication date 04/08/1999) and **Levinson et al.** (US 2006/0052592, publication date 03/09/2006, PCT/US03/19383 filed on 06/20/2003, provisional application No: 60/390,304 filed on 06/20/2002) and **Meazza et al.** (Meazza et al., Expression of two interleukin-15 mRNA isoforms

in human tumors does not correlate with secretion: role of different signal peptides, *Eur J Immunol.* 27(5):1049-54, 1997; this reference has been cited by Applicant in the IDS filed on 08/31/2010), as applied to claims 1, 14, 16, 17, 19, 55, 56, 58-60, 66, 67, 69-71 and 77 above, and further in view of **Aarts et al.** (Aarts et al., Vector-based vaccine/cytokine combination therapy to enhance induction of immune responses to a self-antigen and anti-tumor activity, *Cancer Res.* 62(20):5770-7, 2002). Applicant's arguments filed on 08/04/2011 and on 07/19/2011 have been fully considered and found not persuasive. Previous rejection is ***maintained*** for the reasons advanced on pages 18-21 of the office action mailed on 01/19/2011.

For the clarity of record, the rejection for the reasons advanced on pages 18-21 of the office action mailed on 01/19/2011 is reiterated below.

It is noted that claims 1, 55, and 66 are included in the rejection because claim **15** depends from claim 1, claim **57** depends from claims 1 and 55, and claim **68** depends from claims 1 and 66.

Claim 15 is directed to the nucleic acid molecule of claim 1 incorporated into a viral vector.

Claim 57 is directed to the nucleic acid molecule of claim 55 incorporated into a viral vector.

Claim 68 is directed to the nucleic acid molecule of claim 66 incorporated into a viral vector.

The teachings of Yang et al., Letvin et al., Levinson et al., and Meazza et al. have been discussed in the preceding section of the rejection of claims 1, 14, 16, 17, 19, 55, 56, 58-60, 66,

67, 69-71 and 77 under 35 U.S.C. 103(a) as being unpatentable over Yang et al. in view of Letvin et al., Levinson et al., and Meazza et al.

None of Yang et al., Letvin et al., Levinson et al., and Meazza et al. explicitly teaches the limitation "a viral vector" recited in claims 15, 57, and 68.

With regard to the limitation "limitation "a viral vector" recited in claims 15, 57, and 68, **Aarts et al.** teaches vector-based vaccine/cytokine combination therapy to enhance induction of immune responses to a self-antigen and anti-tumor activity (See title and abstract, Aarts et al., 2002). Aarts et al. teaches various vaccination regimen starting with prime (i.e. initial) administration of a composition comprising a nucleic acid encoding human tumor antigen, carcinoembryonic antigen (CEA), expressed from a *recombinant vaccinia (rV) vector* such that the host develops an immune response against human CEA, followed by multiple subsequent booster vaccinations, which comprise administration of recombinant cytokines including recombinant GM-CSF and IL-2 (See Materials and Methods, and Table 1, Aarts, et al., 2002).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Aarts et al. regarding using a *viral vector*-based vaccine/cytokine combination therapy to enhance induction of immune responses to a self-antigen and anti-tumor activity, into the combined teachings of Yang et al., Letvin et al., Levinson et al., and Meazza et al. directed to an isolated plasmid nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of: (i) a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an IgE signal peptide that is from the same species as the non-IgE protein; and (ii) a nucleic acid sequence that encodes a fusion protein that consists of a non-IgE protein sequences linked to an

IgE signal peptide, wherein the non-IgE protein is an immunomodulating cytokine, to arrive the claimed isolated nucleic acid recited in claims 15, 57, and 68 by substituting a plasmid taught by Yang et al., Letvin et al., and Levinson et al. with a viral vector taught by Aarts et al.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Aarts et al. into the combined teachings Yang et al., Letvin et al., Levinson et al., and Meazza et al. because Aarts et al. specifically teaches using viral vector for expression of cytokine from a DNA vaccine.

There would have been a reasonable expectation of success given (i) successful demonstration of the induction of potent Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-NY1999) and release of various cytokines by T-cells of immunized mice, by the teachings Yang et al. (See Figure 3, Yang et al., 2001), (ii) successful demonstration of IL-2/Ig fusion protein in enhancement of antigp120 immune response elicited by pV1-gp120, by the teachings of Letvin et al. (See Example 8, pages 26-29), and (iii) successful demonstration of human IgE signal peptide in the construction and *in vitro* expression of human IgE tetanus fusion protein, by the teachings of Levinson et al., and (iv) successful demonstration of substitution of the sequence encoding natural human IL-15 signal peptide(s) with the signal peptide from IgVx chain in the IL-15 cDNA results in a significantly higher secretion of biologically active IL-15 (15-30-fold) upon cDNA transfection, by the teachings of Meazza et al., and (v) successful demonstration of expression of cytokine IL-2, GM-CSF enhance induction of immune response to an antigen expressed from a DNA vaccine, by the teachings of Aarts et al..

Thus, the claimed invention as a whole was clearly *prima facie* obvious

Applicant's arguments and Examiner's ***Response to Applicant's arguments*** are the same as documented at the end of maintained rejection of claims 1, 14, 16, 17, 19, 55, 56, 58-60, 66, 67, 69-71 and 77 under 35 U.S.C. 103(a) as being unpatentable over **Yang et al.** (Yang et al., Induction of potent Th1-type immune responses from a novel DNA vaccine for West Nile virus New York isolate (WNV-NY1999). *J Infect Dis.* 184(7):809-16, 2001) in view **Letvin et al.** (WO 99/16466, international publication date 04/08/1999) and **Levinson et al.** (US 2006/0052592, publication date 03/09/2006, PCT/US03/19383 filed on 06/20/2003, provisional application No: 60/390,304 filed on 06/20/2002) and **Meazza et al.** (Meazza et al., Expression of two interleukin-15 mRNA isoforms in human tumors does not correlate with secretion: role of different signal peptides, *Eur J Immunol.* 27(5):1049-54, 1997; this reference has been cited by Applicant in the IDS filed on 08/31/2010).

Conclusion

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

4. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Primary Examiner
Art Unit 1632